

CHEST[®]

Official publication of the American College of Chest Physicians



Hypocapnia and Asthma^{*} : A Mechanism for Breathing Retraining?

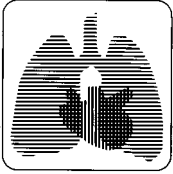
Anne Bruton and Stephen T. Holgate

Chest 2005;127;1808-1811
DOI 10.1378/chest.127.5.1808

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.chestpubs.org/content/127/5/1808.full.html>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2005 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.
(<http://chestjournal.chestpubs.org/site/misc/reprints.xhtml>)
ISSN:0012-3692

A M E R I C A N C O L L E G E O F
 C H E S T
P H Y S I C I A N S[®]



opinions/hypotheses

Hypocapnia and Asthma*

A Mechanism for Breathing Retraining?

Anne Bruton, PhD; and Stephen T. Holgate, DSc

There is some evidence that breathing retraining may be beneficial for patients with asthma, but the mechanism behind this benefit is still unknown. One hypothesis is that individuals can be trained to raise carbon dioxide levels and thereby reverse the bronchoconstrictive effects of hypocapnia and utilize the bronchodilatory effects of hypercapnia. This theory presupposes that individuals with asthma have lower carbon dioxide levels than the healthy population. This article reviews the available evidence supporting the hypothesis and concludes that although attractive, there is currently insufficient evidence to attribute the benefits of breathing retraining to this mechanism. (CHEST 2005; 127:1808–1811)

Key words: asthma; breathing retraining; carbon dioxide; hypocapnia

Abbreviations: ASM = airway smooth muscle; ETCO_2 = end-tidal carbon dioxide

Although pharmacologic therapy remains the primary mode of treatment for patients with asthma, many people also use complementary or alternative therapies. In a recent US study¹ of inner-city children with asthma, 89% of parents questioned reported giving their child some form of complementary therapy, yet only 18% had informed their physician about this. Various forms of breathing retraining have been used as a therapy for patients with asthma in the United States, Europe, and Australia, with some reported benefits,^{2–4} although such benefits have yet to be definitively confirmed. The mechanism behind the reported benefits is currently not known, but one physiologic hypothesis relates to carbon dioxide. The purpose of this article is to draw attention to a theory related to the possible role of carbon dioxide in asthma, and to review the available evidence supporting it.

*From the University of Southampton, Highfield, Southampton, UK.

Dr. Bruton is funded by a Postdoctoral Research Fellowship from the UK Department of Health.

Manuscript received May 17, 2004; revision accepted October 29, 2004.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Anne Bruton, PhD, School of Health Professions & Rehabilitation Sciences, University of Southampton, Highfield, Southampton, SO17 1BJ, UK; e-mail: ab7@soton.ac.uk

SEARCH STRATEGY

Multiple strategies were incorporated to maximize identification of suitable studies. We searched MEDLINE, EMBASE, Cochrane library, CINAHL, and reference lists of original and review articles. Authors of relevant abstracts were contacted to seek additional information.

HYPOCAPNIA

The PaCO_2 reflects the balance between the production and elimination of carbon dioxide. Under normal conditions, the PaCO_2 is maintained at approximately 39 to 41 mm Hg by alveolar ventilation under the control of respiratory centers in the pons and medulla.⁵ Changes in the production of carbon dioxide are usually accompanied by corresponding alterations in alveolar ventilation with little or no change in PaCO_2 . The main physiologic causes for hypocapnia are related to hyperventilation. Mild hypocapnia is not generally associated with any serious effects in healthy individuals, but Laffey and Kavanagh⁶ have proposed that hypocapnia may have a pathogenic role in the development of systemic diseases. However, this suggestion is not new, as it can be found in early writings from the late Russian physiologist, Konstantin Buteyko, during the 1950s.⁷

HYPOCAPNIA AND BRONCHOCONSTRICTION

Although hypocapnia is a consistent finding in acute asthma, it is not certain whether it has any clinically relevant pathogenic role. Proponents of the Buteyko breathing technique⁷ would suggest that this is the case. Also, in 1968 it was hypothesized in the *New England Journal of Medicine*⁸ that hypocapnia during an asthma attack could perpetuate bronchospasm and lead to a cycle of progressive hypocapnia and increasing bronchospasm. There is a body of experimental evidence that supports this hypothesis. There is *in vitro* animal evidence suggesting that low alveolar PCO₂ causes bronchoconstriction,⁹ while a high PCO₂ acts directly on the airway smooth muscle to cause bronchodilatation.¹⁰ There is also *in vivo* animal evidence that hypocapnia increases airway resistance.^{11–13}

In addition, there is support for the association between hypocapnia and bronchoconstriction from experimental evidence from humans.^{14–19} Fisher et al²⁰ and McFadden et al²¹ have shown that a low alveolar carbon dioxide in patients with asthma was associated with increases in airway tone. Van den Elshout et al¹⁹ studied the effects of hypercapnia and hypocapnia on respiratory resistance in both normal and asthmatic subjects. They found that a reduction in end-tidal PCO₂ of only 7.5 mm Hg caused an increase in resistance by 13% and a fall in reactance by 45% in asthmatics, while the same reduction in PCO₂ had no effect on healthy subjects. Conversely an increase in end-tidal PCO₂ of only 7.5 mm Hg resulted in a significant fall in airway resistance in both asthmatic and normal subjects. Bayindir et al²² reported on the adverse effects of hypocapnia during cardiopulmonary bypass, which led to a significant increase in airway resistance and a reduction in lung compliance.

Airway smooth muscle (ASM) is now recognized as being the major end-effector of acute airway narrowing in asthma.²³ The primary function of ASM is to regulate the bronchomotor tone in response to contractile agonists. ASM responsiveness is influenced by both internal and external stimuli; however, it is still unclear whether the airway hyperresponsiveness seen in asthma is primarily due to changes within the smooth muscle itself, or to changes external to the muscle. Possible mechanisms for hypocapnia inducing bronchoconstriction may be through neural reflexes, through increasing blood vessel caliber, through the provocation of mediator release, or through a direct effect on the ASM. A study by Lindeman et al¹³ suggests that hypocapnia has a direct effect on ASM cells, possibly via the effect of intracellular alkalosis on intracellular free calcium concentration. Reynolds and McEvoy⁹ suggested

that in the guinea pig lung, a reduction in alveolar PCO₂ produced an increase in airway resistance by inducing bronchospasm and increasing the permeability of microvessels in the airway, and that this effect was mediated by the release of tachykinins from C-afferent nerves in the airways. However, the mechanism for the bronchoconstriction is still uncertain and may relate to the degree of hypocapnia. Sterling¹⁴ found that when end-tidal PCO₂ was approximately < 30 mm Hg, the bronchoconstriction was mediated via the autonomic nervous system (through the vagus nerve), but that when end-tidal PCO₂ was < 15 mm Hg it was mediated by direct effect on the ASM.

HYPOCAPNIA AND ASTHMA

In 1952, Buteyko theorized that “hidden” hyperventilation is the basic cause of asthma,⁷ linked to the inflammatory and structural changes characteristic of the disease. During acute episodes of asthma, hyperventilation leading to hypocapnia is well documented,^{6,24,25} but very few studies^{19,26,27} have suggested that patients with asthma are hypocapnic when their asthma is stable. In 1988, Hormbrey et al²⁷ compared carbon dioxide response and breathing pattern in patients with asthma, patients with symptomatic hyperventilation, and healthy subjects. The asthmatic group had a significantly higher resting respiratory frequency and minute ventilation, and had lower mean end-tidal carbon dioxide (ETCO₂) [37 mm Hg] than the other two groups (40 mm Hg and 41 mm Hg, respectively). However, there were only six subjects in each group. Van den Elshout et al¹⁹ studied 30 asthmatic and 15 healthy volunteers and also found that the asthmatic group had lower mean resting ETCO₂ when compared to the healthy subjects (36 mm Hg vs 40 mm Hg). Neither of these two studies used matched control subjects. However, more recently, Osborne et al²⁶ studied a group of 23 patients with mild, stable asthma and compared them with a matched control group. Both arterial carbon dioxide and ETCO₂ were found to be significantly lower in the patients with asthma (ETCO₂, 37 mm Hg vs 40 mm Hg). Concomitant evidence for clinically significant hyperventilation in such subjects is not available. Thomas et al²⁸ reported that one third of women and one fifth of men treated for asthma in a single general practice had symptoms suggestive of hyperventilation or “dysfunctional breathing.” However, they used the Nijmegen questionnaire to assess dysfunctional breathing, and some authors^{29,30} have questioned the validity of this questionnaire in identification of hyperventilation in an

asthmatic population because of the potential overlap between the symptoms of anxiety and those of asthma.

If one assumes that the observed hypocapnia in stable asthmatics is due to hyperventilation, it is an attractive proposition that retraining breathing patterns to reduce hyperventilation in such individuals should make it possible to raise carbon dioxide levels. This should theoretically reverse any bronchoconstrictive effects of hypocapnia, and possibly make use of the bronchodilatory effects of hypercapnia. There is some evidence that various forms of breathing retraining (eg, physiotherapy, yoga, and Buteyko) have had some beneficial effects on asthma patients. However, at present it is uncertain what mechanism produces these effects over and above any placebo effect. Apart from the carbon dioxide hypothesis, another potential physiologic mechanism behind breathing retraining is the effect of rhythmic stretching on the ASM.^{31,32} A number of psychological mechanisms are also possible such as increasing feelings of mastery or control, induction of relaxation/meditation, or nonspecific attention effects. A recent randomized controlled trial of the Buteyko breathing technique by Cooper et al⁴ found that Buteyko breathing improved asthma symptoms and reduced bronchodilator use, but without affecting airway caliber or responsiveness. Thomas et al² reported on a study of physiotherapy breathing retraining for asthma patients and found improved quality-of-life scores. However, neither of these studies shed any light on the mechanism producing the improvements generated. Buteyko, physiotherapy, and yoga therapies share very similar breathing techniques that encourage slowing the rate of breathing, and the use of breath holding. Very few studies of breathing therapy have included measures of carbon dioxide in their outcomes. One exception is the randomized controlled trial of Buteyko by Bowler et al,³³ who found no significant differences in means between the intervention and control groups after intervention, but unfortunately do not report any within subject changes. In a controlled trial currently only published in abstract form, Abramson et al³⁴ reported no changes in lung function, but did find some increase in ET_{CO₂} in one group and some reduction in response to carbon dioxide in another. They employed a factorial design involving four groups, one receiving "full" Buteyko (Buteyko practitioner plus Buteyko video), two receiving "partial" Buteyko (Buteyko practitioner plus placebo video, or Buteyko video plus placebo educator), and one receiving no Buteyko (placebo video plus placebo educator). Their findings are interesting, but the complexity of their design makes interpretation difficult.

FUTURE RESEARCH

Although breathing control and breathing training are common interventions for respiratory conditions, there is a paucity of randomized clinical trials examining their effectiveness or the mechanism for any effect. A recent Cochrane review stated that "no reliable conclusions can currently be drawn concerning the use of breathing exercises for asthma in clinical practice."³⁵ However, trends for improvement are encouraging; further large-scale trials, including full descriptions of treatment methods and outcome measurements, are required to establish effectiveness. To establish if the carbon dioxide mechanism plays a role, researchers need first to establish if people with asthma do have significant differences in either absolute level of carbon dioxide or sensitivity to carbon dioxide. There is also a need for some well-designed clinical trials of breathing retraining with carbon dioxide as the primary outcome measure.

CONCLUSION

There is now some evidence that asthmatic individuals have lower levels of carbon dioxide than the healthy population, even when they are stable and asymptomatic. There is also some indirect evidence that a significant proportion of the stable asthmatic population have symptoms of hyperventilation. Physiotherapists and others regularly use breathing retraining techniques to alleviate these symptoms, with some reported benefits. While these may be related to raising an individual's carbon dioxide levels, as has been hypothesized, as yet there is no convincing evidence that this occurs, or that such a goal is either desirable or achievable.

REFERENCES

- 1 Braganza S, Ozuah PO, Sharif I. The use of complementary therapies in inner-city asthmatic children. *J Asthma* 2003; 40:823–827
- 2 Thomas M, McKinley RK, Freeman E, et al. Breathing retraining for dysfunctional breathing in asthma: a randomized controlled trial. *Thorax* 2003; 58:110–115
- 3 Manocha R, Marks GB, Kenchington P, et al. Sahaja yoga in the management of moderate to severe asthma: a randomized controlled trial. *Thorax* 2002; 57:110–115
- 4 Cooper S, Osborne J, Newton S, et al. Effect of two breathing exercises (Buteyko and pranayama) in asthma: a randomized controlled trial. *Thorax* 2003; 58:674–679
- 5 Gluck SL. Acid-base. *Lancet* 1998; 352:474–479
- 6 Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med* 2002; 347:43–53
- 7 Stalmatski A. Freedom from asthma: Buteyko's revolutionary treatment. London, UK: Kyle Cathie Ltd, 1997
- 8 Hypoxemia and hypocapnia in asthma [abstract]. *N Engl J Med* 1968; 278:1068

- 9 Reynolds AM, McEvoy RD. Tachykinins mediate hypocapnia-induced bronchoconstriction in guinea pigs. *J Appl Physiol* 1989; 67:2454–2460
- 10 D'Angelo E, Calderini IS, Tavola M. The effects of CO₂ on respiratory mechanics in anesthetized paralyzed humans. *Anesthesiology* 2001; 94:604–610
- 11 Ingram RH Jr. Effects of airway versus arterial CO₂ changes on lung mechanics in dogs. *J Appl Physiol* 1975; 38:603–607
- 12 Kolbe J, Kleeberger SR, Menkes HA, et al. Hypocapnia-induced constriction of the canine peripheral airways exhibits tachyphylaxis. *J Appl Physiol* 1987; 63:497–504
- 13 Lindeman KS, Croxton TL, Lande B, et al. Hypocapnia-induced contraction of porcine airway smooth muscle. *Eur Respir J* 1998; 12:1046–1052
- 14 Sterling GM. The mechanism of bronchoconstriction due to hypocapnia in man. *Clin Sci* 1968; 34:277–285
- 15 Newhouse MT, Becklake MR, Macklem PT, et al. Effect of alterations in end-tidal CO₂ tension on flow resistance. *J Appl Physiol* 1964; 19:745–749
- 16 Nielsen TM, Pedersen OF. The effect of CO₂ on peripheral airways. *Acta Physiol Scand* 1976; 98:192–199
- 17 O'Cain CF, Hensley MJ, McFadden ER Jr, et al. Pattern and mechanism of airway response to hypocapnia in normal subjects. *J Appl Physiol* 1979; 47:8–12
- 18 Jamison JP, Glover PJ, Wallace WF. Comparison of the effects of inhaled ipratropium bromide and salbutamol on the bronchoconstrictor response to hypocapnic hyperventilation in normal subjects. *Thorax* 1987; 42:809–814
- 19 Van den Elshout FJ, van Herwaarden CL, Folgering HT. Effects of hypercapnia and hypocapnia on respiratory resistance in normal and asthmatic subjects. *Thorax* 1991; 46:28–32
- 20 Fisher HK, Holton P, Buxton RS, et al. Resistance to breathing during exercise-induced asthma attacks. *Am Rev Respir Dis* 1970; 101:885–896
- 21 McFadden ER Jr, Stearns DR, Ingram RH Jr, et al. Relative contributions of hypocarbia and hyperpnoea as mechanisms in postexercise asthma. *J Appl Physiol* 1977; 42:22–27
- 22 Bayindir O, Akpınar B, Ozbek U, et al. The hazardous effects of alveolar hypocapnia on lung mechanics during weaning from cardiopulmonary bypass. *Perfusion* 2000; 15:27–31
- 23 Fredberg JJ. Bronchospasm and its biophysical basis in airway smooth muscle. *Respir Res* 2004; Available at <http://respiratory-research.com/content/5/1/2>. Accessed April 26, 2005
- 24 Rodriguez-Roisin R. Gas exchange abnormalities in asthma. *Lung* 1990; 168(suppl):599–605
- 25 Odhiambo JA, Chwala RD. Arterial blood gases and acid-base status of adult patients presenting with acute severe asthma at Kenyatta National Hospital, Nairobi. *East Afr Med J* 1992; 69:319–322
- 26 Osborne CA, O'Connor BJ, Lewis A, et al. Hyperventilation and asymptomatic chronic asthma. *Thorax* 2000; 55:1016–1022
- 27 Hornbrey J, Jacobi MS, Patil CP, et al. CO₂ response and pattern of breathing in patients with symptomatic hyperventilation, compared to asthmatic and normal subjects. *Eur Respir J* 1988; 1:846–851
- 28 Thomas M, McKinley RK, Freeman E, et al. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001; 322:1098–1100
- 29 Keeley D, Osman L. Dysfunctional breathing and asthma: it is important to tell the difference. *BMJ* 2001; 322:1075–1076
- 30 Ritz T, Bobb C, Edwards M, et al. The structure of symptom report in asthma: a reevaluation. *J Psychosom Res* 2001; 51:639–645
- 31 Fredberg JJ, Inouye D, Miller B, et al. Airway smooth muscle, tidal stretches, and dynamically determined contractile states. *Am J Respir Crit Care Med* 1997; 156:1752–1759
- 32 Shen X, Gunst SJ, Tepper RS. Effect of tidal volume and frequency on airway responsiveness in mechanically ventilated rabbits. *J Appl Physiol* 1997; 83:1202–1208
- 33 Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomized controlled trial. *Med J Aust* 1998; 169:575–578
- 34 Abramson M, Borg B, Doran C, et al. A randomized controlled trial of the Buteyko method for asthma [abstract]. *Int J Immunorehabil* 2004; 6:244
- 35 Holloway E, Ram FS. Breathing exercises for asthma. *Cochrane Database Syst Rev* 2004; CD001277

Hypocapnia and Asthma* : A Mechanism for Breathing Retraining?

Anne Bruton and Stephen T. Holgate

Chest 2005;127; 1808-1811

DOI 10.1378/chest.127.5.1808

This information is current as of March 21, 2010

Updated Information & Services	Updated Information and services, including high-resolution figures, can be found at: http://chestjournal.chestpubs.org/content/127/5/1808.full.html
References	This article cites 31 articles, 20 of which can be accessed free at: http://chestjournal.chestpubs.org/content/127/5/1808.full.html#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://chestjournal.chestpubs.org/content/127/5/1808.full.html#related-urls
Open Access	Freely available online through CHEST open access option
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.chestjournal.org/site/misc/reprints.xhtml
Reprints	Information about ordering reprints can be found online: http://www.chestjournal.org/site/misc/reprints.xhtml
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]